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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,326	06/22/2001	George Weiner	C1039/7052 (AWS)	7237

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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,326	WEINER ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-11,14,15,17-21,24,34,43,56 and 78-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-11,14,15,17-21,24,34,43,56 and 78-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *attachment*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/3/2005 has been entered.

The amendment filed 6/3/2005 is acknowledged. The amendment has been entered. Claims 1, 7-11, 14, 15, 17-21, 24, 34, 43, 56 and 78-104 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Specification

The use of the trademark RITUXIMAB has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 7, 8, 10, 11, 14, 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Winkler et al. (Blood 1999; 94(7), pages 2217-2224; previously cited), for the reasons of record (see Office actions mailed 1/9/03 and 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation expression of a B-cell malignancy surface antigen, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught

by Wooldridge would necessarily upregulate the expression of a B-cell surface antigen because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification).

Wooldridge does not specifically teach that the method can utilizes an antibody specific for a B-cell surface antigen, such as an anti-CD20 antibody, or that the antibody used is specifically C2B8 or Rituximab, or that the oligonucleotide and antibody can be administered together.

Winkler teaches that anti-CD20 antibodies (specifically, Rituximab, which is also referred to as "IDEC C2B8"), can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Winkler in order to make a method for inhibiting the growth of B-CLL lymphoma cells in a subject having B-CLL lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the Rituximab (IDEC C2B8) antibody taught by Winkler, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Furthermore, it would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 1, 7, 8, 10, 11, 14, 17-21 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Winkler et al. (Blood 1999; 94(7), pages 2217-2224; previously cited) and further in view of WO 98/40100 (Davis et al.).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically,

MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation expression of a B-cell malignancy surface antigen, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of a B-cell surface antigen because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification).

Wooldridge does not specifically teach that the method can utilizes an antibody specific for a B-cell surface antigen, such as an anti-CD20 antibody, or that the antibody used is specifically C2B8 or Rituximab, or that the oligonucleotide and antibody can be administered together; nor does Wooldridge teach that the oligonucleotide is ODN 2006 (SEQ ID NO: 729).

Winkler teaches that anti-CD20 antibodies (specifically, Rituximab, which is also referred to as "IDEC C2B8"), can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.)

WO 98/40100 (Davis et al.) teaches an immunostimulatory oligonucleotide that is ODN 2006 (i.e., it is 100% identical to SEQ ID NO: 729), which can be used to stimulate B-cell activation and a therapeutic immune response in a subject (e.g., see the oligonucleotide identified as SEQ ID NO: 6 on page 12 of WO 98/40100, as well as the abstract, paragraph bridging page 1-2, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge in order to make a the claimed method wherein the SEQ ID NO: 6 oligonucleotide taught by WO 98/40100 is used in combination with the antibody taught by Winkler (Rituximab (IDEC C2B8), with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when an immunostimulatory CpG oligonucleotide is used in combination with a therapeutic tumor-specific antibody a synergistic therapeutic effect is achieved. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy. Furthermore, the oligonucleotide taught by WO 98/40100 is an art-recognized equivalent to the oligonucleotide taught by Wooldridge as both oligonucleotides were recognized as therapeutic immunostimulatory oligonucleotides (See MPEP 2144.06-2144.07).

It also would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 1, 7, 9, 10, 14, 17-21 rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756; previously cited) and further in view of Pawade et al. (Histopathology, 1995; 27(2) pages 129-137; previously cited) for the reasons of record (see Office actions mailed 1/9/03 and 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would

necessarily upregulate the expression of CD20 because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification). Furthermore, the oligonucleotide would not hybridize to genomic DNA or RNA under stringent conditions.

Wooldridge does not specifically teach that the method can be used to treat Marginal Zone Lymphoma cells, or using an anti-CD20 antibody (specifically C28B), or that the oligonucleotide and antibody can be administered together.

Taji teaches that anti-CD20 antibodies (specifically, C2B8 antibodies), can be used to inhibit the growth of CD20 positive B-cell lymphoma cells (Specifically, SU-DHL-4 and SU-DHL-6 cells) which express a low level of CD20. Taji teaches that the C2B8 antibodies induce apoptosis in the lymphoma cells which may account for the effectiveness of the C2B8 antibody therapy (e.g., see abstract, etc.).

Pawade teaches that marginal zone lymphoma cells are CD20 positive, indicating that marginal zone lymphoma cells express CD20 antigen.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Taji in order to make a method for inhibiting the growth of marginal zone lymphoma cells in a subject having marginal zone lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the C2B8 antibody taught by Taji, with a reasonable expectation of success. Since Pawade teaches marginal zone lymphoma cells express CD20 antigen, and since Taji teaches that an anti-CD20 antibody (C2B8) can be used to treat CD20-expressing lymphocytes, there is a reasonable expectation of success

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Furthermore, it would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 1, 7, 9, 10, 14, 15, 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of Taji et al. (Japanese Journal of Cancer Research; July 1998; Vol. 89(7), pages 748-756; previously cited) and further in view of US Patent 5,969,135 (Ramasamy et al.; previously cited) for the reasons of record (see Office actions mailed 1/9/03 and 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column), which are known to have a low level of CD20 expression, considering neither the claim nor the specification clearly defines what a "low level of CD20 expression" is. The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77). It is noted that although Wooldridge does not specifically indicate that the oligonucleotide administration results in the upregulation of CD20 expression, Wooldridge does teach administration of 300ug of the oligonucleotide, which is clearly in the dose range disclosed in the specification (see p. 63 lines 10-15 of the specification, which indicates, "doses of the compounds disclosed herein typically range from about 0.1ug to 10mg per administration"). Therefore, administering the oligonucleotide using the method taught by Wooldridge would necessarily upregulate the expression of CD20 because the effective dose taught by Wooldridge is within the range of efficacy contemplated in the specification (see p. 63, lines 10-15 of the specification). Furthermore, the oligonucleotide would not hybridize to genomic DNA or RNA under stringent conditions.

Wooldridge does not specifically teach that the method can be used to B-cell lymphoma cells using an anti-CD20 antibody, specifically C2B8, or that the oligonucleotide comprises an

amino acid backbone modification, or that the oligonucleotide and antibody can be administered together, or that the oligonucleotide comprises an amino acid modified backbone.

Taji teaches that anti-CD20 antibodies (specifically, C2B8 antibodies), can be used to inhibit the growth of CD20 positive B-cell lymphoma cells (Specifically, SU-DHL-4 and SU-DHL-6 cells) which express a low level of CD20. Taji teaches that the C2B8 antibodies induce apoptosis in the lymphoma cells which may account for the effectiveness of the C2B8 antibody therapy. (e.g., see abstract, etc.)

Ramasamy teaches backbone modifications which can be made on therapeutic oligonucleotides in order to improve certain properties of the oligonucleotide, including increasing their stability towards enzymes. Ramasamy specifically teaches that an amino acid residue modification to the backbone of the oligonucleotide is one such modification (e.g., see column 1, lines 35-60; and column 3, lines 33-45, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the methods of Wooldridge and Taji in order to make a method for inhibiting the growth of B-cell lymphoma cells in a subject having B-cell lymphoma cells, comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the C2B8 antibody taught by Taji, wherein the oligonucleotide comprises an amino acid modified backbone, with a reasonable expectation of success. Since Ramasamy teaches that the amino acid backbone modification decreases degradation of the oligonucleotide in vivo, there is a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted

in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Furthermore, it would have been prima facie obvious to perform routine optimization to co-administer the oligonucleotide with the antibody at the same time. As noted in *In re Aller*, 105 USPQ 233 at 235,

> "More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

Therefore, routine optimization is not considered inventive and no evidence has been presented that the selection of the source of the nucleic acid, or that co-administration was other than routine, that results from the optimizations have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Claims 24, 34, 43, 78-81, 83, 84, 86, 90, 91 and 94-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) and further in view of WO 98/40100 (Davis et al.)

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column

and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody or that the B-cell malignancy is B-CLL.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

WO 98/40100 (Davis et al.) teaches an immunostimulatory oligonucleotide that is ODN 2006 (i.e., it is 100% identical to SEQ ID NO: 729), which can be used to stimulate B-cell activation and a therapeutic immune response in a subject (e.g., see the oligonucleotide identified as SEQ ID NO: 6 on page 12 of WO 98/40100, as well as the abstract, paragraph bridging page 1-2, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by WO 98/40100 (specifically the oligonucleotide

disclosed as SEQ ID NO: 6 by Davis) in combination with the CD19, CD20, or CD22 antibodies (as taught by Goldenberg), with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when an immunostimulatory CpG oligonucleotide is used in combination with a therapeutic tumor-specific antibody a synergistic therapeutic effect is achieved. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy. Furthermore, the oligonucleotide taught by WO 98/40100 is an art-recognized equivalent to the oligonucleotide taught by Wooldridge as both oligonucleotides were recognized as therapeutic immunostimulatory oligonucleotides (See MPEP 2144.06-2144.07).

Claims 24, 34, 43, 78-81, 83, 84, 86, 90, 91 and 94-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; 89:2994-2998; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) for the reasons of record (see Office actions mailed on 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody,

specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody or that the B-cell malignancy is B-CLL, or that the specific immunostimulatory CpG oligonucleotide used is ODN 2006 (SEQ ID NO: 729).

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claims 43, 84-86, 88, 89, 90 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) and further in view of Winkler et al. (Blood 1999, previously cited) for the reasons of record (see Office actions mailed on 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Goldenberg does not teach that the anti-CD20 antibody is Rituximab.

Winkler teaches that anti-CD20 antibodies, and specifically, the anti-CD20 antibody Rituximab, can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.) It is noted that Rituximab is an antibody that bind to CD20, thus Rituximab is a specific anti-CD20 antibody.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, it would have also been prima facie obvious to one of ordinary skill in the art to modify the method to use Rituximab as the anti-CD20 antibody with a reasonable expectation of success since Winkler teaches that Rituximab is an anti-CD20 antibody that can be used to treat B-cell malignancies.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claims 43, 84-86, 88, 89, 90, 91 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) and further in view of Winkler et al. (Blood 1999, previously cited) and further in view of WO 98/40100 (Davis et al.)

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL, or that the specific immunostimulatory CpG oligonucleotide used is ODN 2006 (SEQ ID NO: 729).

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Goldenberg does not teach that the anti-CD20 antibody is Rituximab.

Winkler teaches that anti-CD20 antibodies, and specifically, the anti-CD20 antibody Rituximab, can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.) It is noted that Rituximab is an antibody that bind to CD20, thus Rituximab is a specific anti-CD20 antibody.

WO 98/40100 (Davis et al.) teaches an immunostimulatory oligonucleotide that is ODN 2006 (i.e., it is 100% identical to SEQ ID NO: 729), which can be used to stimulate B-cell activation and a therapeutic immune response in a subject (e.g., see the oligonucleotide identified as SEQ ID NO: 6 on page 12 of WO 98/40100, as well as the abstract, paragraph bridging page 1-2, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Davis (i.e. SEQ ID NO: 6 of WO 98/40100 which is 100% identical to the instant claimed SEQ ID NO: 729) in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, it would have also been prima facie obvious to one of ordinary skill in the art to modify the method to use Rituximab as the anti-CD20 antibody with a reasonable expectation of success since Winkler teaches that Rituximab is an anti-CD20 antibody that can be used to treat B-cell malignancies.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, “There was clear synergy between CpG

ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy. Furthermore, the oligonucleotide taught by WO 98/40100 is an art-recognized equivalent to the oligonucleotide taught by Wooldridge as both oligonucleotides were recognized as therapeutic immunostimulatory oligonucleotides (See MPEP 2144.06-2144.07).

Claims 43, 84-89, 90 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited) and further in view of Winkler et al. (Blood 1999, previously cited) and further in view of Pawade et al. (Histopathology, 1995; 27(2) pages 129-137; previously cited).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL or a marginal zone lymphoma.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.)

Goldenberg does not teach that the anti-CD20 antibody is Rituximab.

Winkler teaches that anti-CD20 antibodies, and specifically, the anti-CD20 antibody Rituximab, can be used to inhibit the growth of B-CLL lymphoma cells which express a low level of CD20. (e.g., see abstract, Figure 1, etc.) It is noted that Rituximab is an antibody that bind to CD20, thus Rituximab is a specific anti-CD20 antibody.

Pawade teaches that marginal zone lymphoma cells are CD20 positive, indicating that marginal zone lymphoma cells express CD20 antigen.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells wherein B-cell lymphoma is B-CLL or marginal zone lymphoma, comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, it would have also been prima facie obvious to one of ordinary skill in the art to modify the method to use Rituximab as the anti-CD20 antibody with a reasonable expectation of success since Winkler teaches that Rituximab is an anti-CD20 antibody that can be used to treat B-cell malignancies. Furthermore, because Pawade teaches that marginal zone lymphoma cells are CD20 positive (e.g., see abstract, etc.), it would have also

been prima facie obvious to one of ordinary skill in the art that the method of using CpG oligonucleotide in combination with anti-CD20 antibody could be used to treat marginal zone lymphoma (MZL).

The motivation to make the indicated modification to treat the MZL is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model..." (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claims 34, 82, 102 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited), further in view of Pawade et al. (Histopathology, 1995; previously cited) for the reasons of record (see Office actions mailed on 4/20/04), reiterated below for convenience..

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The

oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-CLL or a marginal zone lymphoma.

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.).

Pawade teaches that marginal zone lymphoma cells are CD20 positive, indicating that marginal zone lymphoma cells express CD20 antigen.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, because Pawade teaches that marginal zone lymphoma cells are CD20 positive (e.g., see abstract, etc.), it would have also been prima facie obvious to one of ordinary skill in the art that the method of using CpG oligonucleotide in combination with anti-CD20 antibody could be used to treat marginal zone lymphoma (MZL).

The motivation to make the indicated modification to treat the MZL is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claims 34, 82, 102, 103 and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of US Patent 6,306,393 B1 (Goldenberg, previously cited), further in view of Pawade et al. (Histopathology, 1995; previously cited) and further in view of WO 98/40100 (Davis et al.).

Wooldridge teaches a method of inhibiting the growth of a B-cell malignancy wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the B-cell malignancy. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach that the method can be used to treat B-cell lymphoma cells using an anti-CD19 or anti-CD22 antibody, or that the B-cell malignancy is B-

CLL or a marginal zone lymphoma, or that the immunostimulatory CpG is ODN 2006 (SEQ ID NO: 729).

Goldenberg teaches immunotherapy of B-cell malignancies using anti-CD19, anti-CD20 and anti-CD22 antibodies (e.g., see abstract, claims 1, 5, 9, 10, 22, etc.). Furthermore, the Goldenberg teaches that said antibodies can be used to treat B-cell malignancies, including B-CLL (e.g., see claims 1, 5, 14, etc.).

Pawade teaches that marginal zone lymphoma cells are CD20 positive, indicating that marginal zone lymphoma cells express CD20 antigen.

WO 98/40100 (Davis et al.) teaches an immunostimulatory oligonucleotide that is ODN 2006 (i.e., it is 100% identical to SEQ ID NO: 729), which can be used to stimulate B-cell activation and a therapeutic immune response in a subject (e.g., see the oligonucleotide identified as SEQ ID NO: 6 on page 12 of WO 98/40100, as well as the abstract, paragraph bridging page 1-2, etc.).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Goldenberg in order to make a method for inhibiting the growth of B-cell lymphoma cells (including B-CLL cells and antibody resistant cells) in a subject having the B-cell lymphoma cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the CD19, CD20, or CD22 antibodies as taught by Goldenberg. Furthermore, because Pawade teaches that marginal zone lymphoma cells are CD20 positive (e.g., see abstract, etc.), it would have also been prima facie obvious to one of ordinary skill in the art that the method of using CpG

oligonucleotide in combination with anti-CD20 antibody could be used to treat marginal zone lymphoma (MZL).

The motivation to make the indicated modification to treat the MZL is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy, including tumor cells resistant to antibody therapy.

Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wooldridge et al. (Blood, 1997; previously cited) in view of Micouin (Leukemia, 1997; previously cited) for the reasons of record (see Office actions mailed on 4/20/04), reiterated below for convenience.

Wooldridge teaches a method of inhibiting the growth of a cancer (B-cell malignancy) wherein an isolated synthetic immunostimulatory oligonucleotide 18 nucleotides long comprising a phosphorothioate modified backbone and an unmethylated CpG motif (see p. 2995, first column and Figure 1) was administered (300ug) to mice comprising the cancer. Specifically, the malignant B-cells are 38C13 lymphoma cells (p. 2995, bottom of first column). The oligonucleotide treatment is followed by administration of a mouse IgG2a monoclonal antibody, specifically, MS11G6 (see p. 2994, last paragraph, the same antibody used in Example 3 of the specification p. 76-77).

Wooldridge does not specifically teach the method can be used to treat cancer using a human or humanized IgG1 isotype antibody.

Micouin teaches that human IgG1 antibodies can be used to treat human leukemia.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the methods of Wooldridge and Micouin in order to make a method for inhibiting the growth of tumor cells in a subject having the tumor cells comprising administering to said subject the immunostimulatory CpG nucleic acid taught by Wooldridge in combination with the human IgG1 isotype antibodies taught by Micouin, with a reasonable expectation of success.

The motivation to make the indicated modification is provided by Wooldridge, who teaches that the when the oligonucleotide was used in combination with the antibody, it resulted in a synergistic effect. Specifically, Wooldridge teaches, "There was clear synergy between CpG ODN and antitumor MoAb in this model…" (See page 2997, first column) Thus indicating that the immunostimulatory CpG oligonucleotides improve the efficacy of antibody anti-tumor therapy.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 100 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. (Emphasis added).

In the instant case, new claim 100 indicates that the surface antigen is not expressed on the malignant B-cells. It is noted that the Applicants have not indicated where in the specification support for the new claim can be found. A thorough search of the specification did not identify a disclosure that the surface antigen is not expressed on the malignant B-cells and which are upregulated in the B-cell malignancy in response to treatment with the CpG oligonucleotides. The specification only appears to disclose that the CpG oligonucleotide upregulates expression of surface antigens that are expressed (albeit at a low level) in the cells of the B-cell malignancy (e.g., see Figure 3). Should Applicants disagree, they are asked to indicate

where support for the new claim can be found in the specification by identifying the particular page and line numbers where support can be found.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claim 1 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11 and 85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 85 contain the trademark/trade name RITUXIMAB. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the

trademark or trade name. In the present case, the trademark/trade name is used to identify/describe an antibody specific for and, accordingly, the identification/description is indefinite.

Response to Arguments

Applicant's arguments filed 6/3/2005 have been fully considered but they are not persuasive.

Applicants argue that claims 1, 24, 34 and 43 (the independent claims) have been amended to include the limitation that the B-cell malignancy upregulate expression of an antigen in response to immunostimulatory CpG oligonucleotide and that the antibody is specific for the upregulated antigen. Applicants assert that they made the unexpected discovered that administration of an immunostimulatory CpG oligonucleotide induces the expression of certain cell surface antigens, including CD19, CD20 and CD22, and that the induction of these antigens lends itself to enhanced antibody-dependent cellular cytotoxicity (ADCC) directed toward malignant cells expressing these particular antigens. Applicant assert that they have made the unexpected discovery that administration of an immunostimulatory CpG nucleic acid to malignant B cells lacking or having only low level expression of certain antigens upregulates expression of the antigens, resulting in an unexpectedly efficient antibody response. Applicants also contend that the cited references do not teach or suggest that the immunostimulatory CpG oligonucleotides can upregulate expression of the surface antigens on the B-cell malignancy; and therefore, one of skill in the art would not have been motivated to combine the references to make the claimed invention.

In response, the prior art teaches that immunostimulatory CpG oligonucleotides enhance the efficacy of tumor-specific therapeutic antibodies (e.g., see Wooldridge et al.). For example, Wooldridge teaches that using an immunostimulatory CpG ODN in combination with an antitumor antibody result in a synergistic effect with respect to antibody dependent cellular cytotoxicity [ADCC]. Specifically, Wooldridge explicitly teaches, "There was a clear synergy between CpG ODN and antitumor MoAb in this model and the most likely explanation for this finding is enhanced ADCC." (see p. 2997, first column).

Furthermore, the effect of the immunostimulatory CpG oligonucleotide on the B-cell lymphoma does not appear to specifically upregulate expression of particular B-cell lymphoma antigens. Rather, the instant disclosure appears to indicate that the administration of the immunostimulatory CpG oligonucleotides non-specifically increase expression of all B-cell lymphoma surface antigens (e.g., see Figure 3 of the instant Application).

Therefore, since the method of treating a B-cell lymphoma using an immunostimulatory oligonucleotide in combination with a anti-tumor antibody that is specific for a B-cell lymphoma surface antigen is prima facie obvious (for the reasons indicated above), and since the amount of immunostimulatory CpG oligonucleotide taught in the prior art (Wooldridge) is sufficient to on-specifically up regulate expression of B-cell lymphoma surface antigens, any anti-tumor antibody specific for a B-cell lymphoma surface antigen (such as C2B8, RITUXIMAB, etc.) would necessarily be an antibody that is specific for the B-cell lymphoma surface antigen that is upregulated in response to the immunostimulatory oligonucleotide.

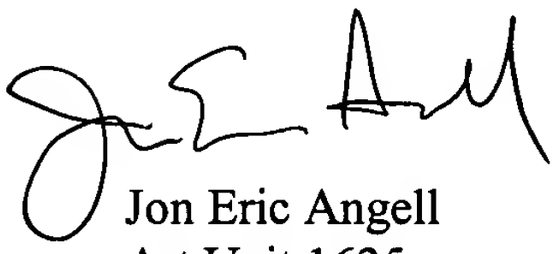
Therefore, Applicants arguments are not persuasive.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jon Eric Angell
Art Unit 1635

GenCore version 5.1.6

OM nucleic - nucleic search, using sw model

Run on: August 5, 2005, 06:17:01 ; Search time 268 Seconds
(without alignments)
530.126 Million cell updates/sec

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Scoring table: OLIGO_NUC
Gapop 60.0 , Gapext 60.0

Searched: 4390206 seqs, 2959870667 residues

Word size : 0

Total number of hits satisfying chosen parameters: 8780412

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Listing first 45 summaries

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9: geneseqn2003bs:*
10: geneseqn2003cs:*
11: geneseqn2003ds:*
12: geneseqn2004as:*
13: geneseqn2004bs:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
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4	24	100.0	24	2	AAZ41936	Aaz41936 IL-12 sec
5	24	100.0	24	2	AAV83715	Aav83715 Synthetic
6	24	100.0	24	2	AAV74252	Aav74252 CpG-N mot
7	24	100.0	24	3	AAZ61001	Aaz61001 Nucleotid
8	24	100.0	24	3	AAZ48012	Aaz48012 Immune re
9	24	100.0	24	3	AAZ47876	Aaz47876 Immunosti
10	24	100.0	24	3	AAA39265	Aaa39265 CpG immun
11	24	100.0	24	3	AAZ47671	Aaz47671 Parasitic
12	24	100.0	24	3	AAA63588	Aaa63588 Immune st
13	24	100.0	24	3	AAA63586	Aaa63586 Immune st
14	24	100.0	24	3	AAA63598	Aaa63598 Immune st
15	24	100.0	24	3	AAC60280	Aac60280 Immunosti
16	24	100.0	24	3	AAA93700	Aaa93700 Unmethyla
17	24	100.0	24	4	AAC87240	Aac87240 CpG oligo
18	24	100.0	24	4	AAC87232	Aac87232 Immunosti
19	24	100.0	24	4	AAC87231	Aac87231 5'-amidat
20	24	100.0	24	4	AAC87233	Aac87233 Immunosti
21	24	100.0	24	4	AAC87227	Aac87227 Methylate
22	24	100.0	24	4	AAC87234	Aac87234 Digoxigen
23	24	100.0	24	4	AAC87237	Aac87237 5'-amidat
24	24	100.0	24	4	AAC87222	Aac87222 Immunosti
25	24	100.0	24	4	AAH50616	Aah50616 Cytokine
26	24	100.0	24	4	AAF98866	Aaf98866 CpG immun
27	24	100.0	24	4	AAF98732	Aaf98732 Human IFN
28	24	100.0	24	4	AAF98830	Aaf98830 CpG immun
29	24	100.0	24	4	AAF85631	Aaf85631 Vaccine a
30	24	100.0	24	4	AAF59508	Aaf59508 Immunosti
31	24	100.0	24	4	AAF99173	Aaf99173 Immunosti
32	24	100.0	24	4	AAF99146	Aaf99146 Immunosti
33	24	100.0	24	4	AAF99760	Aaf99760 Immunosti
34	24	100.0	24	4	AAF99762	Aaf99762 Immunosti
35	24	100.0	24	4	AAF99135	Aaf99135 Immunosti
36	24	100.0	24	4	AAF99224	Aaf99224 Immunosti
37	24	100.0	24	4	AAF99284	Aaf99284 Immunosti
38	24	100.0	24	4	AAF99759	Aaf99759 Immunosti
39	24	100.0	24	4	AAF99283	Aaf99283 Immunosti
40	24	100.0	24	4	AAF99761	Aaf99761 Immunosti
41	24	100.0	24	4	AAF99119	Aaf99119 Immunosti
42	24	100.0	24	4	AAH44490	Aah44490 CpG adjuv
43	24	100.0	24	5	AAS08982	Aas08982 CpG-conta
44	24	100.0	24	6	ABK48091	Abk48091 CpG oligo
45	24	100.0	24	6	ABS78483	Abs78483 Angiogene

ALIGNMENTS

RESULT 1
AAV60953
ID AAV60953 standard; DNA; 24 BP.
XX
AC AAV60953;
XX
DT 14-DEC-1998 (first entry)
XX
DE Unmethylated cytosine-guanine dinucleotide containing oligonucleotide 4.
XX
KW ss; unmethylated CpG dinucleotide; immune response; natural killer cell;
KW Th2 response; Th1 response; Th1 cytokine; hepatitis B.
XX
OS Synthetic.
XX
PN WO9840100-A1.
XX
PD 17-SEP-1998.
XX
PF 10-MAR-1998; 98WO-US004703.
XX
PR 10-MAR-1997; 97US-0040376P.
XX
PA (OTTA-) OTTAWA CIVIC LOEB RES INST.
PA (QIAG-) QIAGEN GMBH.
PA (IOWA) UNIV IOWA RES FOUND.
XX
PI Davis HL, Schorr J, Krieg AM;
XX
DR WPI; 1998-520792/44.
XX
PT Use of oligonucleotides containing an unmethylated CpG dinucleotide -
PT useful as, e.g. adjuvant with antigen, or nucleic acid encoding antigen
PT for inducing immune response in subject.
XX
PS Disclosure; Page 12; 67pp; English.
XX
CC Oligonucleotides containing at least 1 unmethylated CpG dinucleotide
CC affect the immune response in a subject by activating natural killer
CC cells or redirecting a subject's immune response from a Th2 to a Th1
CC response by inducing monocytic and other cells to produce Th1 cytokines.
CC These nucleic acids containing at least 1 unmethylated CpG can be used as
CC an adjuvant, specifically to induce an immune response against an

ATTACHMENT (PAGE 2 of 2)

CC antigenic protein, and are used particularly for virally mediated
CC disorders, e.g. hepatitis B virus infection
XX
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Query Match 100.0%; Score 24; DB 2; Length 24;
Best Local Similarity 100.0%; Pred. No. 0.0018;
Matches 24; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

Qy 1 TCGTCGTTTTGTCGTTTTGTCGTT 24
||||||||||||||||||||||||
Db 1 TCGTCGTTTTGTCGTTTTGTCGTT 24 - SEQ ID NO: 6 of WO98/49100

RESULT 2